Poster 3826

Results from the completed dose escalation of the hematological arm of the phase I THINK study evaluating multiple infusions of NKG2D-based CAR T-cells as standalone therapy in relapsed/refractory acute myeloid leukemia and myelodysplastic syndrome patients

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BACKGROUND

- The rapid approval of two anti-CD19 **chimeric antigen receptor** (CAR) T-cell therapies and advanced development of anti-BCMA CAR T-cell therapies demonstrate the potential of the approach in B-cell malignancies. However, targets with a similar profile for CAR T-cell therapy in other diseases including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are lacking.
- **CYAD-01** is an **autologous CAR T-cell** therapy engineered with a multi-complex, **second-generation NKG2D CAR** comprising the full-length human natural killer group 2D (NKG2D) receptor fused to the intracellular domain of CD3ζ.
- The **NKG2D** receptor targets 8 ligands (MHC class I chain related proteins A [MICA] and B [MICB] and unique long 16 binding proteins [ULBP] 1–6 ligands) found at high frequency across a range of malignancies. Interestingly, non-malignant cells within the tumor microenvironment (myeloid-derived suppressor cells, regulatory T-cells and neo-endothelial cells) also express NKG2D ligands which led in preclinical models to the induction by CYAD-01 of a broader anti-tumor response beyond direct cancer cell killing.
- **CYAD-01** is being evaluated in relapsed/refractory (r/r) AML/MDS patients, with the objective to define whether the optimal CYAD-01 treatment is with prior preconditioning chemotherapy (DEPLETHINK study, poster 3844) or without any pretreatment (THINK study, here discussed).

THINK STUDY

- The open-label Phase I **THINK study** (NCT03018405) evaluates multiple administrations of CYAD-01 in r/r AML, MDS and multiple myeloma (MM) patients without any prior non-myeloablative preconditioning or bridging therapy.
- **The study design**:
  - Dose escalation segment with a Fibonacci 3+3 design evaluating (i) **three dose levels** (DL) of CYAD-01: $3x10^8$ (DL-1), $1x10^9$ (DL-2), and $3x10^9$ (DL-3) cells per infusion, and (ii) **two administration schedules** for the 1st cycle of 3 CYAD-01 infusions: every two weeks (**biweekly schedule**) or weekly (**dose dense schedule**). The dose dense schedule evaluates only the $1x10^9$ (DL-2) and $3x10^9$ (DL-3) cells per infusion.
  - Expansion segment with the selected dose and schedule.
- Potential new cycle of treatment (3 infusions every two weeks) in the absence of progression at the end of the first cycle ($1x10^9$ or $3x10^9$ cells/infusion).
- **Primary endpoint** of the dose escalation segment is the occurrence of dose-limiting toxicity (DLT) during the CYAD-01 treatment phase. Patients who have not completed their first cycle of CYAD-01 administrations for other reasons than DLT should be replaced. Key secondary endpoints include additional safety parameters, objective responses, duration of responses, and CYAD-01 cell kinetics.

STUDY STATUS

- 25 patients have been enrolled so far in the dose escalation segment (ongoing).
- Safety analysis is presented for the total treated patient population who received at least one CYAD-01 infusion, including three MM patients enrolled at the DL-1 biweekly schedule. Clinical activity and cells engraftment are presented for the 22 r/r AML/MDS patients.

TABLES & FIGURES

Table 1: Patient characteristics

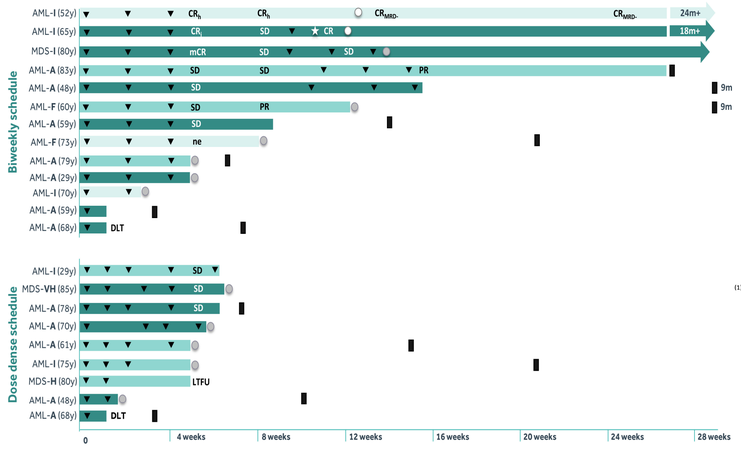
Data cut-off: 19 November 2019	Biweekly schedule DL-1 $3x10^8$ N=6	Biweekly schedule DL-2 $1x10^9$ N=3	Biweekly schedule DL-3 $3x10^9$ N=7	Biweekly schedule Total N=16	Dose dense schedule DL-2 $1x10^9$ N=4	Dose dense schedule DL-3 $3x10^9$ N=5	Dose dense schedule Total N=9
Age (years): Mean (Range)	64.8 (52-79)	74.0 (60-83)	60.1 (29-80)	64.5 (29-83)	61.3 (29-80)	69.8 (48-85)	66.0 (29-85)
Gender: Male/Female	5/1	2/1	6/1	13/3	1/3	3/2	4/5
ECOG performance score at screening (Grade 0/1/2)	2/4/0	2/1/0	2/5/0	6/10/0	2/2/0	0/4/1	2/6/1
LVEF (%): Mean (Range)	58.8 (48-66)	64.7 (55-79)	61.3 (55-67)	61.0 (48-79)	58.8 (52-65)	56 (50-60)	57.2 (50-65)
Tumor type							
r/r Acute Myeloid Leukemia	3	3	6	12	3	4	7
De novo	2	2	5	9	3	2	5
AML MRC/secondary AML	1	1	1	3	0	2	2
r/r Myelodysplastic Syndrome	0	0	1	1	1	1	2
r/r Multiple Myeloma	3	0	0	3	0	0	0
ELN 2017/R-IPSS Risk Stratification for AML/MDS							
Favorable (AML)/Intermediate (MDS)	1/0	1/0	0/1	2/1	0/0	0/0	0/0
Intermediate (AML)/High-Risk (MDS)	2/0	0/0	1/0	3/0	2/1	0/0	2/1
Adverse (AML)/Very High-Risk (MDS)	0/0	2/0	5/0	7/0	1/0	4/1	5/1
Bone marrow blasts (%) mean (range)	9.5 (0.0-21.0)	27.3 (9.8-48.2)	12.2 (4.0-20.0)	14.0 (0.0-48.2)	41.5 (15.0-82.0)	37.5 (9.0-58.0)	39.3 (9.0-82.0)
Platelets (10^3/µL) mean (range)	127.7 (22.0-261.0)	101.3 (63.0-144.0)	53.6 (6.0-157.0)	90.3 (6.0-261)	72.0 (39.0-159.0)	45.4 (24.0-74.0)	57.2 (24.0-159.0)
ANC (10^3/µL) mean (range)	2.13 (0.0-8.1)	1.28 (0.14-3.46)	1.27 (0.09-2.59)	1.6 (0.0-8.1)	0.66 (0.12-2.08)	0.58 (0.18-0.99)	0.6 (0.1-2.1)

Table 2: Incidence of treatment-related adverse events (AEs) reported at least once as ≥ Grade 3

Data cut-off: 19 November 2019	Biweekly schedule DL-1 ($3x10^8$) 6 patients (15 inf.)			Biweekly schedule DL-2 ($1x10^9$) 3 patients (12 inf.)			Biweekly schedule DL-3 ($3x10^9$) 7 patients (24 inf.)			Biweekly schedule Total 16 patients (51 inf.)			Dose dense schedule DL-2 ($1x10^9$) 4 patients (15 inf.)			Dose dense schedule DL-3 ($3x10^9$) 5 patients (15 inf.)			Dose dense schedule Total 9 patients (30 inf.)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Patients with at least 1 related AE (N.%)	6 (100%)	-	1 (17%)	3 (100%)	2 (67%)	-	6 (86%)	1 (14%)	3 (43%)	15 (94%)	3 (19%)	4 (25%)	4 (100%)	-	1 (25%)	3 (60%)	2 (40%)	1 (20%)	7 (78%)	2 (22%)	2 (22%)
Cytokine release syndrome (CRS)	1 (17%)	-	-	2 (67%)	2 (67%)	-	4 (57%)	-	1 (14%) [1]	7 (44%)	2 (13%)	1 (6%)	3 (75%)	-	-	3 (60%)	2 (40%) [1]	1 (20%)	6 (67%)	2 (22%) [1]	1 (11%)
Hypoxia	1 (17%)	-	1 (17%)	3 (100%)	-	-	-	-	-	4 (25%)	-	1 (6%)	1 (25%)	-	-	-	-	-	1 (11%)	-	-
Pneumonitis	1 (17%)	-	1 (17%)	-	-	-	-	-	-	1 (6%)	-	1 (6%)	-	-	-	-	-	-	-	-	-
Fatigue	2 (33%)	-	-	-	-	-	1 (14%)	1 (14%)	-	3 (19%)	1 (6%)	-	-	-	-	-	-	-	-	-	-
Headache	-	-	-	-	-	-	1 (14%)	1 (14%)	-	1 (6%)	1 (6%)	-	-	-	-	-	-	-	-	-	-
Infusion related reaction	1 (17%)	-	-	-	-	-	-	-	-	1 (6%)	-	-	1 (25%)	-	1 (25%)	-	-	-	1 (11%)	-	1 (11%)
Pain in extremity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1 (20%)	1 (20%)	-	1 (11%)	1 (11%)	-
Lymphopenia	1 (17%)	-	1 (17%)	1 (33%)	-	-	1 (14%)	-	1 (14%)	3 (19%)	-	2 (13%)	-	-	-	-	-	-	-	-	-
Thrombocytopenia	-	-	-	1 (33%)	1 (33%)	-	1 (14%)	-	1 (14%)	2 (13%)	1 (6%)	1 (6%)	-	-	-	-	-	-	-	-	-

[1] Dose-limiting toxicity (DLT)

Figure 1: Time to response and duration of treatment in AML/MDS patients



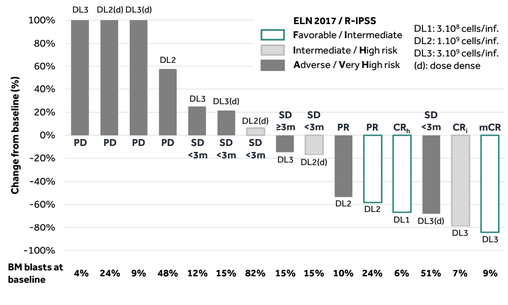
ELN 2017 (AML) / R-IPSS (MDS)
Favorable / Intermediate
Intermediate / High risk
Adverse / Very High risk

$3x10^8$ cells/infusion
$1x10^9$ cells/infusion
$3x10^9$ cells/infusion
CYAD-01

Disease Progression
Death
AlloHSCT
Salvage chemotherapy

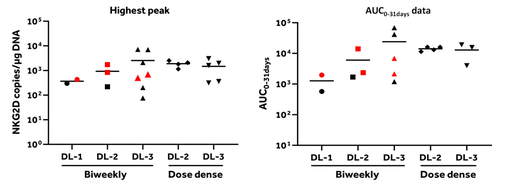
AlloHSCT: allogeneic human stem cell transplant; CR: complete remission; CR_L: CR with incomplete hematologic recovery; CR_H: CR with partial hematologic recovery; CR_{MRD-}: CR without minimal residual disease; DLT: dose-limiting toxicity; ELN: European LeukemiaNet; LTFU: lost to follow-up; mCR: marrow CR; m: month; ne: non-evaluable; PD: progressive disease; PR: partial remission; R-IPSS: Revised International Prognostic Scoring System; SD: stable disease

Figure 2: Best change in BM blast count from baseline in AML/MDS patients (%) [1]



[1] Evaluable patients for whom the first planned bone marrow evaluation or an early documented bone marrow in case of progressive disease was performed. Seven patients, including two patients with dose-limiting toxicity at the first CYAD-01 infusion, did not have post-baseline bone marrow data available and therefore are not reported on the graph

Figure 3: CYAD-01 kinetics in the peripheral blood



Red dots indicate the patients in CR/PR. AUC: area under the curve

AUC was calculated using the linear trapezoidal rule. The number of copies of the transgene per µg of genomic DNA isolated from PBMCs and measured by digital droplet PCR at prespecified timepoints was used. AUC is reported from the time of first dosing to 31 days.

MAIN RESULTS

- **Patient demographics and tumor characteristics** are summarized in Table 1.
  - It is interesting to note an apparent imbalance in certain clinical attributes between the two CYAD-01 administration schedules arms. Patients (pts) enrolled onto the dose dense schedule appear to have a higher average bone marrow (BM) blast count and lower average platelet and neutrophil counts suggestive of greater cancer disease burden and pancytopenic status at baseline as compared to pts enrolled in the biweekly schedule.
- The **patient incidence of treatment-related adverse events** (AEs) (CARTOX grading for cytokine release syndrome (CRS), NCI-CTCAE, Version 5.0 for other AEs) is summarized in Table 2.
  - An encouraging safety profile was observed with 11 pts out of 25 with Grade (G) 3/4 treatment-related AEs. The dose dense schedule did not modify the overall safety profile so far.
  - CRS occurred in 13 pts with four G3 and two G4 events, which resolved with tocilizumab treatment. No treatment-related neurotoxicity AEs were reported.
  - There were two DLTs at $3x10^9$ (DL-3) cells per infusion, one CRS G4 DLT in the biweekly schedule (24 infusions) and one CRS G3 DLT with the dose dense schedule (15 infusions - cohort ongoing).
- Encouraging **anti-leukemic activity** was observed in 8 pts with BM blasts decrease including 5 objective responses and 1 SD for ≥ 3 months according to the ELN2017 recommendations (AML) or Revised IPSS (MDS) (Figure 2).
  - One of these pts presenting a SD for < 3months died of infectious disease at Day 50 with a 68% BM blast decrease after the 1st cycle of 3 CYAD-01 infusions (Day 32).
  - Most responses, with the exception of the two pts bridging to an allograft procedure, were of short durability (Figure 1).
  - Albeit with insufficient patient numbers to enable a statistical conclusion, the anti-leukemic activity appeared predominantly observed in pts in the non-Adverse ELN2017 (AML)/non-Very High R-IPSS (MDS) risk stratification categories.
- There was some evidence of dose-dependence engraftment of CYAD-01 cells (Figure 3). However, there was no strong evidence of correlation of dose with clinical activity in the study to date.

CONCLUSIONS AND PERSPECTIVES

- The current results support a good safety profile of a multiple dose schedule with CYAD-01 without prior preconditioning chemotherapy in r/r AML/MDS patients.
- The **anti-leukemic activity rate**, although mostly of short durability, is promising in such refractory patient population. Even if the overall sample size of this Phase I study is small, this clinical activity does not seem to be correlated to the dose-levels and is predominantly observed in the non-Adverse ELN2017/non-Very High R-IPSS risk stratification categories.
- The clinical activity data obtained recently with the dose dense schedule cohorts did not demonstrate an improvement of the clinical outcome. However, it is important to outline that these last enrolled pts presented with greater BM blasts infiltration and apparent more profound pancytopenic status at baseline than the first enrolled patients who received the biweekly schedule. Whether this blunted CYAD-01 activity remains open to question.
- Given the tolerability and short-term clinical activity of CYAD-01, efforts have been made to optimize the manufacturing process ("OptimAb") under the same IND, to enrich for early memory phenotype CAR T-cells that showed enhanced anti-tumor activity in preclinical models (poster 3844).
- Further recruitment into the THINK trial will use the OptimAb manufacturing process.

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